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Emerging Options in the Treatment of Bipolar Disorders

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Abstract

Bipolar disorder is a common and severe condition, and has a clinical outcome that is frequently sub-optimal. Only a small number of therapeutic options are currently available for the disorder. A growing range of novel therapeutic options for the treatment of bipolar disorder are under investigation. These include the anticonvulsants, atypical antipsychotics and options such as the omega-3 fatty acids and transcranial magnetic stimulation. Of the anticonvulsants, lamotrigine is currently the agent for which the greatest amount of controlled clinical data is accumulating, particularly in the depressed and rapid cycling phases of the illness. Olanzapine is currently the atypical antipsychotic with the largest body of evidence in mania, although data is emerging on other atypical antipsychotics including risperidone and ziprasidone. Data regarding the atypical agents in other phases of the illness are awaited. The options available for this difficult to treat condition is increasing with the new range of agents.

Bipolar disorder is a severe and recurrent disorder, with a lifetime prevalence estimated at 1.6 to 1.8%. The illness is associated with significant morbidity and mortality, and has pervasive effects in most spheres of life.[1] There are a limited number of standard treatments, including lithium, valproic acid (valproate) and carbamazapine, and even these do not have the full range of clinical effects necessary in bipolar disorder.

Of additional concern is that current studies of outcomes in this illness are far from optimal. Tohen et al.[2] followed 75 patients postmania over a 4-

year period who were receiving standard treatment. Only 28% were in remission, 72% had at least 1 episode of mania or depression, and there was a 4% mortality rate in the study. Keck et al.[3] studied the course of 134 patients for a year on standard treatment. Syndromal recovery occurred in 48% of the sample and full syndrome resolution only in 26%. Of substantial concern is that functional recovery was present in a mere 24% of these patients.

Suicide rates in patients with bipolar disorder are estimated at 10 to 19%, with a greater risk in males, and in the mixed, psychotic and depressive phases of the disorder. There is clearly an urgent need for additional therapeutic options.

This review summarises data on the newer and emerging therapeutic options for patients with bipolar disorder, which include anticonvulsants, atypical antipyschotics, omega-3 fatty acids, and electroconvulsive therapy (ECT) and transcranial magnetic stimulation. A literature search was conducted on Medline which was augmented by manual searches of key words.

1. Anticonvulsants

1.1 Lamotrigine

Lamotrigine is perhaps the best studied novel anticonvulsant in bipolar disorder. It has a diverse range of mechanisms of action, including inhibition of voltage-dependant sodium channels, inhibition of excitatory amino acids such as glutamate and aspartate, and calcium antagonism. It may also block serotonin 5-HT_3 receptors and act to potentiate dopaminergic transmission.[4,5]

A chart review study of lamotrigine in patients with treatment-resistant bipolar disorder suggested effectiveness.[6] Lamotrogine was also effective in a nonblind 48-week study of 75 patients with treatment-resistant bipolar disorder.[7] In addition, nonblind data has suggested a role for lamotrigine in rapid cycling bipolar disorder.[8-10] However, in a placebo-controlled study in patients with rapid cycling no significant treatment difference was found where time to intervention was the primary outcome measure.[11] Nevertheless, in this study, significantly more patients on lamotrigine with bipolar II disorder were still in the study than those on placebo. 41% of lamotrigine patients versus 26% of placebo patients ($p = 0.03$) were stable without relapse for 6 months of monotherapy. Frye et al.[12] reported that in a group of patients with predominantly rapid cycling, lamotrigine was superior to both placebo and gabapentin. Walden et al.[13] found an equivalent outcome in patients with rapid cycling in a small ($n = 14$) study comparing lithium and lamotrigine.

Nonblind studies have suggested that lamotrigine may have an antidepressant effect.[14,15] In a double-blind study of 437 patients with unipolar depression, both lamotrigine 200 mg/day and desipramine 200 mg/day were differentiated from placebo on the Clinical Global Impression Scales (CGI) of Severity of Illness (CGI-S) and of Improvement (CGI-I) but not on the 17-item Hamilton Rating Scale for Depression (HAM-D)[16] at week 8. In a double-blind, placebo-controlled study of 195 patients with bipolar depression, lamotrigine at doses of 50 and 200 mg/day showed significant efficacy on the Montgomery Åsberg Rating Scale (MADRS). However, the HAM-D scale, which was chosen as the primary outcome measure, did not differentiate between the groups.[17]

Case reports suggesting the use of lamotrigine in refractory mania are available.[18] A small ($n = 30$) randomised, controlled trial comparing lamotrigine and lithium in acute hospitalised patients with mania found equivalent efficacy between the 2 treatments.[19,20] Because of the need for slow dose escalation, lamotrigine is not a practical option for the treatment of mania. Nevertheless, efficacy in the manic phase is of theoretical importance in establishing efficacy in multiple phases of the illness in order to fulfil various definitions of a mood stabiliser.

Lamotrigine has been investigated in related conditions, including schizoaffective disorder, where case reports of efficacy are published,[21] as well as borderline personality disorder, which is argued by the authors to have some relation to bipolar disorder.[22]

This increasing body of clinical data suggests that lamotrigine has substantial potential in the therapy of bipolar disorder. The results of longer term maintenance trials are awaited, and will more clearly define the role of this agent.

1.2 Topiramate

Topiramate is an anticonvulsant that augments γ-aminobutyric (GABA)ergic neurotransmission as well as having glutamate antagonist properties. The drug has been a focus of clinical interest in bipolar disorder, not least because it is associated with weight loss.[23] However, of concern is a reported rate of emergence of depression of around 15% in epilepsy trials, and depression is listed as an adverse event in the US package insert in 8% of patients at a dosage of 220 to 400 mg/day and 13.4% of patients receiving 600 to 1000 mg/day.[24] In addition, there are case reports of the emergence of psychotic symptoms in patients with epilepsy treated with topiramate.[25]

There are a number of case reports[26] and nonblind studies suggesting topiramate may be effective in bipolar disorder. Marcotte[27] retrospectively reported a benefit in 62% of 58 outpatients. McElroy et al.[28] in a nonblind study of 54 patients suggested efficacy, particularly in patients with rapid cycling and mania. A nonblind on-off study of 10 patients with mania suggested the drug was effective.[29] In a randomised, single-blind comparison of topiramate and sustained release bupropion (amfebutamone) added to a mood stabiliser in patients with bipolar depression, the 2 drugs were of comparable efficacy.[30]

However, the only available controlled data on topiramate in mania are negative and as yet unpublished.[31] This was a recently completed, industry-sponsored, multicentre, double-blind, placebo-controlled study of the safety and efficacy of topiramate in the treatment of acute manic or mixed episodes. The primary outcome measure was improvement in patients with bipolar I disorder on the Young Mania Rating Scale (YMRS). Secondary outcome measures included the Brief Psychiatric Rating Scale, MADRS, CGI and Global Assessment.

Given the absence of a consistent positive body of data to date, further data from controlled clinical trials are necessary to define the potential clinical role of topiramate in bipolar disorder.

1.3 Gabapentin

Gabapentin has also attracted attention as a potential therapeutic agent in bipolar disorder. Its primary mechanism of action is to increase brain GABA levels in a dose-dependant manner. Importantly, it lacks any propensity to dependence and tolerance, unlike the benzodiazepines. Its attractiveness is increased by the most benign adverse event profile of the newer anticonvulsants.

A number of encouraging nonblind studies with gabapentin have been reported, in indications such as treatment refractory disorder, mania depression, mixed states and rapid cycling.[32-40] However, a placebo-controlled trial of adjunctive therapy with gabapentin 900 to 3600 mg/day in patients with bipolar I disorder who were in either a manic, hypomanic or mixed state has been reported by Pande et al.[41] In this study, the response to placebo (n = 59) was significantly greater than that to gabapentin (n = 58) on the YMRS, and no differences between the groups emerged on the HAM-D or any other secondary outcome measures. Similarly, in a double-blind crossover study by Frye and colleagues in patients with refractory mood disorders,[12] the CGI response rates were 52% for lamotrigine, 26% for gabapentin and 23% for placebo. However, no controlled data on gabapentin in maintenance or the depressive phase of the disorder are available. The negative trial results to date do not support a clear role for gabapentin in bipolar disorder.

However, there appears to be accumulating evidence of the efficacy of gabapentin in anxiety disorders.[42]

1.4 Others

A double-blind, placebo-controlled trial suggesting efficacy of phenytoin in combination with

haloperidol in mania has been reported. The authors suggest that efficacy of phenytoin maybe related to inhibition of voltage-gated sodium channels.[43] There are a number of novel anticonvulsants that are likely to be targets for future investigation. The first case reports of utility of tiagabine have appeared in the literature.[44,45] However, a nonblind case series of 8 patients with mania showed no efficacy and significant adverse events.[46] Cases of aggravation of mania[47] and utility with zonisamide in mania in a nonblind case series[48] have been reported. Other novel anticonvulsants such as remacemide may be future targets of investigation.

It may be prudent to note that the mechanism whereby certain anticonvulsants have efficacy in bipolar disorder is poorly understood. In addition, it is unlikely that the mechanisms underpinning efficacy in seizures will overlap with those responsible for efficacy in mood disorders. Anticonvulsants differ substantially in their mechanisms of action, and it would be most unlikely if efficacy in any of the phases of bipolar disorder would turn out to be a class effect of anticonvulsants.

2. Atypical Antipsychotics

There have recently been developments in the use of the new atypical antipsychotic drugs for the treatment of bipolar disorder. These new agents will be individually discussed here and the data supporting their use in dipolar disorder reviewed. The situation is changing so rapidly that even recent reviews of the newer agents have already become dated.[49,50]

2.1 Olanzapine

Olanzapine has recently been approved by the US Food and Drug Administration (FDA) for use in acute mania. Two double-blind, placebo-controlled trials have appeared in the literature.[51,52] These 2 studies involved patients in the manic, rapid cycling and mixed phases of the illness either with or without psychotic features. According to these 2 studies, efficacy superior to placebo was demonstrated by olanzapine for the treatment of mania. Statistically significant differences between olanzapine and placebo were demonstrated in week 3 in one trial and week 1 in the other. In these 2 studies response rates were 48.6 and 64.8% for olanzapine versus 24.2 and 42.9% for placebo, respectively. Drop-out rates due to 'lack of efficacy' were 28.6% in the olanzapine group and 47.8% in the placebo group ($p = 0.02$).

Both trials had a short wash-out period (1 to 4 days). The effect of abrupt medication discontinuation in bipolar illness is documented and this phenomenon could have had a greater effect on the placebo groups than on the active treatment arm of the study.[53]

There was no significant difference in the treatment of psychotic versus nonpsychotic patients with mania with either olanzapine or placebo in the first study. It has been previously documented that patients with psychotic mania will respond similarly to patients with non-psychotic mania if treated with mood stabilisers.[54] The results in the second study[52] showed a high placebo response of 43% and an olanzapine response of 65% on the YMRS.

Olanzapine did not induce depressive symptoms in either study. Only in the second study did olanzapine show a statistically significant improvement in depressive symptoms as measured on the 21-item HAM-D scale ($p = 0.05$). Olanzapine displayed few extrapyramidal adverse effects with results not significantly different to placebo despite the high doses used. This finding is significant given the sensitivity of bipolar patients to the development of these symptoms.[55]

A further comparative study with olanzapine in mania has also been published. Berk et al.[56] compared olanzapine with lithium in a small trial of 4 weeks' duration and found no statistically significant difference in efficacy between the 2 agents. To date, no controlled data exist for the use of olanzapine in bipolar depression or maintenance. Rothschild et al.[57] showed some bipolar patients who were psychotically depressed did respond to olanzapine. Mania induction by olanzapine seems to be very rare but has been documented in isolated cases.[58-61]

Further study is clearly needed to elucidate the precise role of olanzapine in the treatment of this complex disorder, particularly in the maintenance and depressive phases of the disorder.

2.2 Risperidone

Very little controlled data exist for the use of risperidone in bipolar disorder. The first double-blind controlled trial (Segal et al.[62]) compared risperidone 6mg daily to lithium and haloperidol in mania. No significant differences between the 3 groups were noted except for the induction of extrapyramidal adverse effects in which risperidone and haloperidol were not statistically significantly different. This suggests that the dose of risperidone may need to be lower in bipolar mood disorder.

Sachs[63] compared add-on risperidone 1 to 6 mg/day, haloperidol 2 to 12 mg/day or placebo in 158 patients who were receiving either lithium or valproic acid for the management of acute mania. Risperidone was superior to placebo as measured by the YMRS and CGI at end-point (3 weeks) compared with placebo. Tohen et al.[64] and Ghaemi et al.[65] added risperidone to other mood-stabilising agents and found it to be effective. Ghaemi and Sachs[66] looked at the 6-month follow-up of risperidone (mean dose 2.75 mg/day) addition to other medications patients with bipolar disorder. They found no mania induction in this nonblind study and 50% of these patients showed improvement. However, there are cases of induction of mania with risperidone.[67-71] Clearly much further study with this agent is needed.

2.3 Quetiapine and Ziprasidone

To date no controlled studies have been published on the use of quetiapine in bipolar illness. A number of nonblind studies have been published.[72-75] In these reports quetiapine seems to have been effective and well tolerated at doses ranging from 40.4 to 425 mg/day. Data from controlled trials are needed.

A 3-week, double-blind, placebo-controlled trial of ziprasidone in mania has been published.[76] Significant differences in the MRS score were reported with ziprasidone (n = 131) versus placebo (n = 64) at all time-points after baseline.

3. Novel Therapeutic Options

3.1 Omega-3 Fatty Acids

Inhibition of neuronal signal transduction systems is a common mechanism amongst mood stabilisers. Omega-3 fatty acids dampen phosphatidyl inositol and arachidonic acid mediated signal transduction. In addition, there is now evidence of impaired phospholipid metabolism and impaired fatty acid-related signal transduction processes in both depression and bipolar disorder.[77]

In a small (n = 30) 4-month, double-blind, placebo-controlled trial comparing omega-3 fatty acids with olive oil, in addition to treatment as usual, there was a significantly longer period of remission in the omega-3 group.[78] These data, while preliminary, offer a promising new avenue of investigation in this disorder.

3.2 Electroconvulsive Therapy and Transcranial Magnetic Stimulation

ECT has a long history of utility in bipolar disorder.[79] In addition to unequivocal efficacy in the depressive phase of the disorder, there is extensive evidence of antimanic efficacy.[80] Furthermore, there is some evidence of the efficacy of maintenance ECT (M-ECT), given monthly, in treatment-refractory patients with bipolar disorder.[81,82] Because of logistical constraints and ongoing public concerns regarding ECT, it is an option that remains low in most treatment algorithms.

Transcranial magnetic stimulation (TMS) is a promising research tool with potential therapeutic uses in mood disorders. Early researchers reported transient mood effects on patients receiving this form of treatment for neurological disorders and suggested further investigations. Controlled trials of TMS in major depression suggest that it may be a promising avenue for future investigation in bipolar disorder.[83,84]

In a 14-day, double-blind trial of 16 patients with mania, a significant improvement in patients

receiving right prefrontal TMS was seen. This may imply laterality opposite to its effect in depression.[85] Although much remains to be elucidated regarding the mechanism, technique and efficacy of TMS, it appears to be a potentially fruitful candidate for further research.

3.3 Others

Vagus nerve stimulation has shown some promise in depression, including resistant bipolar depression, and maybe another possibility for future research.[86] Tamoxifen, a protein kinase C inhibitor, was studied in a single-blind case series of 7 patients. The mean decrease in Y-MRS scores was 10.29, and 5 of the 7 patients exhibited a >50% decrement in scores. Further controlled data is anticipated.[87]

4. Conclusion

A range of new therapeutic options is under investigation for the treatment of bipolar disorder. Most of these are agents adopted from the armamentarium of other disorders. A poor understanding of the basic pathophysiology of bipolar disorder hampers the search for therapeutic options. Nevertheless, there is a growing number of candidate options. While some of these may not survive the rigours of adequate double-blind, controlled studies, the list of options for this difficult-to-treat condition is certain to grow.

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